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EXAMINER

SWOPE, SHERIDAN

ART UNIT	PAPER NUMBER
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1652

DATE MAILED: 10/03/2003

16

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/940,235

Applicant(s)

SAHNI ET AL.

Examiner

Sheridan L. Swope

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 30 June 2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-3 and 32 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-3 and 32 is/are rejected.
- 7) ☒ Claim(s) 1-3 and 32 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

DETAILED ACTION

Applicant's response, on June 30, 2003, Paper No. 15, to the first Office Action on the Merits of this case is acknowledged. It is acknowledged that applicants have amended Claims 1-3 and 32 and cancelled Claims 4-31. Claims 1-3 and 32 are hereby reconsidered.

Figure Legends

Objection to the figure legend for Fig 7 is maintained, as the changes requested in the prior action have not been made. Corrections are required.

Claim Rejections - 35 USC § 112-Second Paragraph

Rejection of Claim 32 under 35 U.S.C. 112, second paragraph, as being indefinite for the reasons described in the prior action is maintained, as corrections have not been made.

Claim Rejections - 35 USC § 112-First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

In this regard, the application disclosure and claims are compared per the factors indicating in the decision re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). These factors are considered when determining whether there is sufficient evidence to support a description that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. The factors include but are not limited to: (1) the nature of the invention; (2) the breath of the claims; (3) the predictability or unpredictability of the art; (4) the amount of direction or guidance presented; (5) the presence or absence of working examples; (6) the quantity of experimentation necessary; (7) the relative skill of those skilled in the art.

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Each factor is here addressed on the basis of comparison of the disclosure, the claims, and the state of the prior art in the assessment of undue experimentation.

Rejection of Claims 1-3 and 32 under 35 U.S.C. 112, first paragraph is maintained. The specification does not reasonably provide enablement for any modified hybrid plasminogen activator comprising any modified streptokinase and any pair of modified fibrin binding domains derived from domains 4 and 5 or 1 and 2 of human fibronectin. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 1-3 and 32 are so broad as to encompass any modified hybrid plasminogen activator comprising any modified streptokinase and any pair of modified fibrin binding domains, derived from domains 4 and 5 or 1 and 2 from human fibronectin. The scope of these claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of hybrid plasminogen activators broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired plasminogen activation and fibrin binding requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the protein's structure relates to its function. However, in this case the disclosure is limited to the hybrid plasminogen activators encoded by the sequences set forth in Figs 17b, 19b, 21b, and 22b.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the results of such modifications are unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of Claims 1-3 and 32 which encompass any hybrid plasminogen activator comprising any modified streptokinase and any modified pair of fibrin binding-domains derived from domains 4 and 5 or 1 and 2 of human fibronectin. The specification does not support the broad scope of Claims 1-3 or 32 because the specification does not establish: (A) the structure of all modified fibrin binding domains that may be used in the recited utility; (B) the structure of all modified streptokinases that may be used in the recited utility; (C) the structure of all modified hybrid plasminogen activators that may be used in the recited utility; (D) regions of all hybrid plasminogen activators' structure which may be modified without effecting the plasminogen activation or fibrin binding; (D) the general tolerance of the plasminogen activation and fibrin binding functions to modification and extent of such tolerance; (E) a rational and predictable scheme for modifying any residues with an expectation of obtaining the desired biological function; and (F) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any number of hybrid plasminogen activators with an enormous number of amino acid modifications of any streptokinase and an enormous number of amino acid modifications of the fibrin binding-domains derived from domains 4 and 5 or 1 and 2 of human fibronectin. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of the identity of sequences having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir, 1988).

Applicants provide the following reasons to argue that the specification enables the hybrid proteins of Claims 1-3 and 32. That, the enablement question was not analyzed according to Wands, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988). That, the analysis provided by the Examiner would require sequence-limited claims in every DNA or protein application. That, working examples can support a generic claim. That, the rejection ignores advances in the art that are now decades old, enabling the art to synthesize variants of the claimed (known) fibrin-binding domains and screen them for fibrin binding. That, streptokinase has been well characterized for many years. These arguments are not found to be persuasive for the following reasons.

The Wands factors have now been listed at the beginning of the rejection of Claims 1-3 and 32 under 35 U.S.C. 112, first paragraph. Each factor has been addressed on the basis of

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comparison of the disclosure, the claims, and the state of the prior art in the assessment of undue experimentation.

To enable a person of ordinary skill in the art to make and use an invention, the specification and/or knowledge of the art must provide said person sufficient information on the structure and function of any protein or DNA molecule recited so that they can make and use the invention without undue experimentation. Claims reciting modified proteins or DNA molecules with no guidance as to the parent sequence to be modified or which modifications can and cannot be made and obtain the desired utility do not enable a person of ordinary skill in the art to make and use the invention without preparation of essentially infinite numbers of modified molecules and extensive testing of said molecules. Such efforts are undue. For the instant application, the specification and knowledge in the art fail to describe the modified hybrid plasminogen activators in such a way as to allow a person of ordinary skill in the art to make and use the recited molecules.

It is acknowledged that working examples can support a generic claim; however, the working examples must provide sufficient guidance to allow a person of ordinary skill in the art to make and use the complete scope of the recited invention. The hybrid plasminogen activators as encoded by the sequences set forth in Figs 17b, 19b, 21b, and 22b are insufficient to provide enablement for the scope of recited hybrid plasminogen activators, which is essentially infinite.

It is acknowledged that there have been advances in the art, which enable the mutagenesis and testing of proteins. However, the number of modified hybrid plasminogen activators recited by the scope of the instant invention, which is essentially infinite, makes the preparation and testing, without guidance, undue experimentation.

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It is acknowledged that streptokinase has been known in the art for some time. Malke et al, 1987, Kim et al, 1996, and Fay et al, 1998 all teach that the C-terminal 41 amino acid residues are dispensable for streptokinase activity. Malke et al, 1987 teach that the N-terminal 42 amino acid residues are dispensable for streptokinase activity, while, in contrast, Lee et al, 1999 teach that Valine¹⁹ is important for streptokinase activity and Fay et al teach that Valine¹³ and Valine²⁰ are necessary for streptokinase activity. (All references provided by Applicants). Said teachings are not sufficient to enable a person of ordinary skill in the art to make and use all the modified hybrid plasminogen activators recited by the instant claims. The effect of replacement of any amino acid residue in a protein can be unpredictable. Wishart et al, 1995 teach that a single mutation of a Gly residue to a Cys residue (G¹²⁰C) converts a phosphotyrosine binding-domain into a dual-specificity phosphatase (Fig 4). While, as taught by Witkowski et al, 1999, a single mutation of a Cys residue for a Gln residue (C¹⁶¹Q) converts a β -ketoacyl synthase to a malonyl decarboxylase (Fig 3). Thus, the effects of even a single mutation on a protein's activity and function are unpredictable. The specification and the current state of the art fail to provide sufficient guidance to enable a person of ordinary skill in the art to make and use the recited scope of modified hybrid plasminogen activators without undue experimentation to modify any hybrid plasminogen activator and test the effect of the modification on the desired utility. For these reasons, and those state above, rejection of Claims 1-3 and 32 under 35 U.S.C. 112, first paragraph is maintained.

Rejection of Claims 1-3 and 32 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed,

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had possession of the claimed invention, for the reasons described in the prior action, is maintained.

Applicants provide the following arguments to prove that the specification sufficiently describes the recited invention of Claims 1-3 and 32. That, the Office has failed to conduct the analysis required in the MPEP§2163; specifically that for analysis of a genus, a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. That, the application as filed is clear that Applicants intended an invention encompassing an SK component linked to various fibrin binding components in various configurations. That, the plasminogen activation-function of the SK component is lagged or delayed. The four examples of this delay are representative and those in the art would understand that the inventors were in possession of the claimed invention. These arguments are not found to be persuasive for the following reasons.

The specification teaches the structure of only four representative species of hybrid plasminogen activator proteins. Disclosure of the structures of said representative species is insufficient to describe the structure of all the modified hybrid plasminogen activators recited by the scope of the instant invention, which is essentially infinite.

It is acknowledged that, in the application as filed, it is clear that Applicants intended an invention encompassing an SK component linked to various fibrin-binding components in various configurations. However, the description of an invention as “encompassing an SK component linked to various fibrin binding components in various configurations” is insufficient. The phrase “an SK component” provides no description of the structure of all SK components

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encompassed. The phrase “various fibrin binding components” provides no description of the structure of all fibrin-binding components encompassed. The phrase “various configurations” provides no description of the structure of all configurations encompassed. Within said argument, Applicants have acknowledged that their invention is not sufficiently described in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

It is acknowledged that the instant application describes the function of the hybrid plasminogen activators as having a lag before plasminogen activation. The Office has not rejected Claims 1-3 and 32 for lack of written description on the function of the recited hybrid plasminogen activators. Claims 1-3 and 32 have been rejected under 35 U.S.C. 112, first paragraph because the specification fails to sufficiently describe the structure of the recited hybrid plasminogen activators.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Rejection of Claims 1-3 and 32 under 35 U.S.C. 103(a) as being unpatentable over Brown et al, 1992 in view of Malke, 1990 (IDS) and further in view of Atkinson et al, 1998, for the reasons described in the prior action, is maintained.

Applicants provide the following arguments to support their request for withdrawal of this rejection. That, to establish a prima facie case of obviousness, ...there must be some

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suggestion or motivation, either in the references themselves or the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. That, it is not at all clear why one skilled in the art would modify the structure of Malke et al, which already includes kringle domains to bind fibrin, by adding further fibrin binding domains. There is simply no motivation to do that. That, the invention provides an unexpected advantage: the claimed single-peptide hybrid provides a desirable delay in plasminogen activation that is not taught in any way in Brown or Malke. That, Atkinson is cited as a tertiary reference, regarding formulations and is not relevant to this issue. These arguments are not found to be persuasive.

Any person of ordinary skill in the art would know that preparation of a recombinant fusion protein comprising the N- or C-terminal fibrin-binding domains of fibronectin fused to streptokinase would be easier and safer to prepare than a molecule comprising said fibrin binding domains chemically cross-linked to streptokinase. Therefore, any person of ordinary skill in the art would be motivated to use the recombinant methods of Malke et al, to prepare said fusion protein, which comprises the components of the crossed-linked protein of Brown et al.

The rejection of Claims 1-3 and 32 under 35 U.S.C. 103(a) in the prior action did not state that one would be motivated to modify the structure of Malke et al, which already includes kringle domains to bind fibrin, by adding further fibrin binding domains. Said rejection stated that it would be obvious to a person of ordinary skill in the art to use the methods of Malke et al to prepare a fusion protein, which comprises the components of the crossed-linked protein of Brown et al.

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The functional features of a protein are inherent to its structure. The delay in activation of the hybrid plasminogen activator made obvious by the teachings of Brown et al in view of Malke et al, is inherent to said hybrid plasminogen activator. Furthermore, said lag is detected by the experiment shown in Table 6; Brown et al teaches that their conjugate, comprising streptokinase cross-linked to fibrin-binding domains of fibronectin, has 50% less activity at 2-6 mins, compared to unconjugated streptokinase.

It is acknowledged that Atkinson is cited as a tertiary reference regarding formulations. Atkinson et al is relevant because it teaches that pharmaceutical compositions comprising stabilizers, as recited in Claim 32, are common in the art.

NEW ISSUES

Claims-Objections

Claim 1-3 are objected to for poor grammatical construction and language.

In Claim 1, line 4, –portions of a SK– should be changed to –fragments of a SK–.

In Claim 1, line 10, –wherein,– should be inserted before –the hybrid plasminogen activator–.

In Claim 1, line 10, –possessing– should be changed to –possesses–.

In Claim 1, line 11, –independently– should be deleted.

In Claim 1, line 11, –exhibiting– should be changed to –exhibits–.

In Claim 1, line 13, there should be a comma after –lag–.

In Claim 2 on line 2, the phrase –is bound with– should be changed to –is linked to–.

In Claims 2 and 3, the phrase –as claimed in Claim 1– should be set off by commas.

In Claim 2, line 4, after – 1 and 2– there should be a comma.

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Additional objections to the claims are as follows.

Claim 3 is objected to because the current claim set indicates that Claim 3 is currently amended. But the current Claim 3 is identical to the original Claim 3.

Claim 32 is objected to because the marked-up version of the current amended claim does not show all the changes.

Claim 32 is objected to for including a single hard bracket,].

Claim 2 is objected to for failing to further limit Claim 1, from which it depends.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.


Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sheridan L. Swope whose telephone number is 703-305-1696. The examiner can normally be reached on M-F; 9:30-7 EST.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached on 703-308-3804. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Sheridan L. Swope, Ph.D.


REBECCA E. PROUTY
PRIMARY EXAMINER
~~GROUP 1000~~
1600